424 Rec'd PCT/PTO 20 JUL 2000

Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER C75087
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/600673
INTERNATIONAL APPLICATION NO. PCT/US99/01377	INTERNATIONAL FILING DATE 21 January 1999	PRIORITY DATE CLAIMED 23 January 1998
TITLE OF INVENTION CELLULOSE DERIVATIVES AND COLORECTAL CANCER RISK REDUCTION		
APPLICANT(S) FOR DO/EO/US Bruce Paul Daggy, Kenneth G. Mandel		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [x] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [x] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [x] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. [x] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [x] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
    [x] Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT US99/01377, filed 21 January 1999, which claims benefit from the following Provisional Applications, 60/072,370, filed 23 January 1998.

14. [ ] A substitute specification.

15. [ ] A change of power of attorney and/or address letter.

16. [ ] Other items or information:

US APPLICATION NO. (if known see 37 CFR 1.50) 09/600673	INTERNATIONAL APPLICATION NO. PCT/US99/01377	ATTORNEYS DOCKET NO. C75087

17. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO **$840.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) **$670.00**		
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$690.00**		
Neither International Preliminary Examination Fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$970.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$96.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0.00**	

Claims	Number Filed	Number Extra	Rate		
Total claims	**18 - 20 =**	**0**	**0 x $18.00**	**$0.00**	
Independent claims	**2 - 3 =**	**0**	**0 x $78.00**	**$0.00**	
Multiple dependent claims (if applicable)			**+ $260.00**	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$96.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
SUBTOTAL =				**$96.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				**$**	
TOTAL NATIONAL FEE =				**$96.00**	
				Amount to be refunded	$
				charged	$

a. ☐ A check in the amount of $____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$96.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
SMITHKLINE BEECHAM CORPORATION
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5017
Facsimile (610) 270-5090

SIGNATURE
Dara L. Dinner
NAME
33,680
REGISTRATION NO.

EXPRESS MAIL LABEL NO.: EL229505120US
MAILED: 20 July, 2000

Attorney Docket No: C75087

IN THE UNITED STATES INTERNATIONAL EXAMINING AUTHORITY

International Application No.:	PCT/US99/01377
International Filing Date:	21 January 1999
Priority Date Claimed:	23 January 1998
Applicant for DO/US:	Bruce P. DAGGY and Kenneth G. MANDEL
Title of Invention:	Cellulose Derivatives and Colorectal Cancer Risk Reduction

Assistant Commissioner for Patents
Box PCT
Att: DO/US
Washington D.C. 20231

FIRST PRELIMINARY AMENDMENT

Sir:

Preliminary to calculating the filing fees and examination of this application, please enter the following remarks and amendments into the record.

In the Specification:

Please enter on the first page under the title the following:

-- This application is the § 371 national stage entry of PCT/US99/01377, filed 21 January 1999, and which claims the benefit of provisional application 60/072,370, filed 23 January 1998. --

In The Claims:

Please amend the following claims:

Claim 3, line 12, after "Claim 1", please delete "or 2".

Claim 4, line 15, after "Claim 1", please delete "or 2".

Claim 5. (Amended) The method according to [any of Claims 1 to 4] Claim 2 wherein the water soluble, non-fermentable cellulose derivative is methylcellulose or hydroxypropyl-methylcellulose.

Claim 12, line 9, after "Claim 10", please delete "or 11".

Claim 13, line 12, after "Claim 10", please delete "or 11".

Claim 14. (Amended) The method according to [any of Claims 10 to 13] claim 10 wherein the water soluble, non-fermentable cellulose derivative is methylcellulose or hydroxypropyl-methylcellulose.

REMARKS

This Preliminary Amendment is being made upon entry of International Application No. PCT/US99/01377 into the U.S. national phase of prosecution The claims have been amended to remove multiple dependencies. No new matter is believed added.

Respectfully submitted,

Dara L. Dinner
Attorney for Applicant
Registration No. 33,680

SMITHKLINE BEECHAM CORPORATION
Corporate Intellectual Property UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Phone (610) 270-5017
Facsimile (610) 270-5090

CELLULOSE DERIVATIVES AND COLORECTAL CANCER RISK REDUCTION

FIELD OF INVENTION

The present invention is directed to the risks associated with colorectal cancers and dietary components.

BACKGROUND OF THE INVENTION

Colorectal cancer is a common and serious medical condition. The incidence of colon cancer is roughly the same in men and women; rectal cancer is somewhat more common in men. Epidemiological studies have shown that when populations have migrated from areas of low incidence (e.g., Eastern Europe or Asia) to an area of higher incidence (the U.S.), their incidence of colorectal cancers increases to U.S. rates within 10-15 years. This suggests that dietary factors play a role in the incidence of colorectal cancers. Indeed, various epidemiological studies which have attempted to relate diet composition to relative risk of colon cancer. Dietary fat intake appears to be positively correlated to risk. Dietary fiber also appears to play a role, although this may not be true for all types of fiber. The epidemiological studies may produce inconsistent results because they do not control for all components for the diet. For example, are high fiber diets protective because foods high in fiber also tend to be low in fat and high in antioxidants? Despite such difficulties in interpreting the data, many health authorities have recommended that dietary fiber intake be roughly doubled to 25-30 g/day. This objective is reflected in the National Academy of Science health goal calling for individuals to consume five or more servings of fruit and six or more servings of breads, cereals and legumes every day. [References for above: Committee on Diet & Health, Food & Nutrition Board, Commission on Life Sciences, National Research Council. Diet and Health. Implications for Reducing Chronic Disease Risk. National Academy Press, Washington, D.C., 1989; and R. B. Sause. 1995. Health Implications of Dietary Fiber. US Pharmacist, Feb. issue.]

Animal studies employing known colon carcinogens have enabled researchers to study dietary components under more controlled conditions. These studies have shown the protective effects for certain sources of insoluble fiber (e.g., wheat bran) and certain soluble, fermentable fibers (e.g., psyllium), as well as other dietary

components such as calcium and certain vitamins [Alabaster et al., Dietary fiber and the chemoprotective modulation of colon carcinogenesis. Mutat Res 1996 Feb 19; 350(1):185-197.] Some studies have shown increased protection from combining wheat bran and psyllium in a colon cancer model [Alabaster et al., Cancer Lett 1993 Nov 30;75(1):53-58] and in a breast cancer model [Cohen et al., J Natl Cancer Inst 1996 Jul 3;88(13):899-907.].

However a need still exists for additional dietary components for the prophylactic treatment of colorectal cancers.

SUMMARY OF THE INVENTION

The present invention is to a method of reducing the incidence of colorectal cancers in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a water soluble, non-fermentable cellulose derivative, alone or in combination with an insoluble fiber and/or a soluble fermentable fiber.

DETAILED DESCRIPTION OF THE INVENTION

The protective effects of water soluble, non-fermentable cellulose derivatives (e.g., methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropyl-methylcellulose) for use as a dietary component for colon cancer risk reduction appears to have not been the subject of previous studies in this area. These semi-synthetic fibers have been in the food supply for decades, and are considered safe, but the beneficial clinical effects of these fibers have rarely been considered outside the area of laxation.

Some studies have investigated the ability of cellulose derivatives to lower plasma cholesterol or improve glycemic control, but have not been used in cancer models, except as vehicles to suspend poorly soluble carcinogens. These fibers have properties which are unique relative to the naturally occurring food fibers. They are 100% water soluble (in cool water; they become insoluble in hot water), and they are non-fermentable. Naturally occurring soluble fibers such as pectin, psyllium, and guar gum, are fermentable in the human GI tract, essentially completely in the case of pectin or guar, and to a significant extent (~50%) in the case of psyllium.
It has been hypothesized that the fermentation products, particularly the short chain fatty acid butyrates, may be responsible for the protective effect of these soluble fibers. However, there are additional proposed mechanisms which would result in cellulose derivatives showing this benefit. These include, but are not limited to, dilution of carcinogens in the GI tract, and decreasing residence time of carcinogens

in the GI tract (either by speeding transit of carcinogens or by elimination of pro-carcinogens prior to their conversion to carcinogens). Both the dilution and faster transit effects are caused by the ability of the fibers to resist degradation and hold water. The gut contents are made both bulkier and softer through this action, and the propulsive motility of the gut is more effective with softer material. Therefore, the water-soluble cellulose derivatives (e.g., methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose) would show a benefit in reducing the incidence of colon cancers.

The present invention has found, unexpectently that the combination of psyllium plus wheat bran was less effect than wheat bran alone or in combination with a water soluble cellulose derivative, such as methylcellulose. This combination of methylcellulose and wheat bran is more effective that the widely accepted protective fiber, and better than the previously published combination therapy. Furthermore, the present invention, as shown below, also supports the proposition that enhanced protection is obtained by use of methylcellulose alone.

BIOLOGICAL EXPERIMENTS

Standard animal models may be employed to demonstrate the protective effect of cellulose derivatives against colon and other cancers.

Experimental and epidemiological evidence suggest that increased dietary fiber is associated with decreased breast cancer risk. Little is known about the role played by different types of fiber and, particularly, mixtures of soluble and insoluble fibers similar to those consumed by human populations in reducing breast cancer risk. High intake of fiber may suppress bacterial hydrolysis of biliary estrogen conjugates to free (absorbable) estrogens in the colon and thus may decrease the availability of circulating estrogens necessary for the development and growth of breast cancers.

Example 1

An example of one such published colon tumor study as applied to psyllium and wheat bran is shown below. Using this model, but with methylcellulose, alone or in combination with wheat bran is proposed. The primary measure to demonstrate the benefit thereof would be the number of preneoplastic aberrant crypt foci.

Alabaster et al., Cancer Lett 1993 Nov 30;75(1):53-58 Potential synergism between wheat bran and psyllium: enhanced inhibition of colon cancer, whose disclosure is incorporated by reference herein in its entirety.

Using this model, but modifying to include methylcellulose instead of psyllium, the following study compares the influence of high fat (20% w/w) diets that combine low levels of calcium (0.18% w/w) and low (1% w/w), medium (4% w/w) and high (8% w/w) levels of dietary fiber from wheat bran (WB), with high (8% w/w or >) levels of dietary fiber from a water soluble cellulose derivative (WS) alone or in various combinations with WB, on the induction of colon tumors in Fischer-344 rats following exposure to azoxymethane (AOM). The rats are fed the experimental diets for 2 weeks, and then are given two subcutaneous. injections of AOM (15 mg/kg body wt./week). Twenty-three weeks following the first injection of AOM, the incidence of colon tumors in the different dietary groups (12 rats/group) is compared.

In the Alabaster study, results showed that by increasing the dietary fiber concentration of WB from 1 to 8% significantly reduced the number of colon tumors/group. When the influence of 8% dietary fiber from WB on the development of colon tumors was compared with that of psyllium (PS) (WB:PS = 0:100), no significant difference was observed. However, combinations of WB and PS showed a greater protective effect than either WB or PS alone, at comparable levels of dietary fiber. The 50:50 combination of WB and PS showed maximum protection, while 25:75 and 75:25 combinations both produced intermediate effects. None of the diets showed any significant effect on the normal growth of rats. The results indicate that WB and PS fiber alone, and to a greater degree in combination, can offer protection against colon cancer promoted by high fat, low calcium diets.

Therefore, diets that include wheat bran in combination with a water soluble cellulose derivative could be an effective means of reducing colon cancer risk in human populations addicted to high risk western diets.

Example 2

The protective benefit in breast cancer of water soluble fibers could be demonstrated with a study design such as the following. The primary efficacy measures would be total tumor number and multiplicity of mammary adenocarcinomas.

A suitable model for this is the study is shown in Cohen et al., J Natl Cancer Inst 1996 Jul 3;88(13):899-907 Wheat bran and psyllium diets: effects on N-methylnitrosourea-induced mammary tumorigenesis in F344 rats, whose disclosure is

incorporated by reference herein in its entirety. Using this model but instead substituting a suitable water soluble fiber as taught herein.

This study can evaluate the effect of wheat bran (an insoluble fiber) and a water soluble cellulose (a soluble fiber) alone and in combination on overall estrogen status, on fecal bacterial beta-D-glucuronidase (a key diet-responsive estrogen-deconjugating enzyme) activity, and on the induction of mammary tumors in rats treated with N-methylnitrosourea (MNU).

Methods: One hundred fifty virgin female F344 rats are fed the NIH-07 diet from 28 days of age until 50 days of age; they are then given a single dose (40 mg/kg of body weight) of MNU by tail vein injection. Three days later, they are randomly assigned to one of five experimental dietary groups (30 animals per group). Soft, white wheat bran (45% dietary fiber content) and water soluble cellulose is added to a modified (high-fat) American Institute of Nutrition (AIN)-76A diet at the following percents, respectively: 12% + 0% (group 1), 8% + 2% (group 2), 6% + 3% (group 3), 4% + 4% (group 4), and 0% + 6% (group 5). Blood, urine, and feces are collected and analyzed by radioimmunoassay techniques for estrogens. Cecal contents are analyzed for bacterial beta-D-glucuronidase activity. After 19 weeks on the experimental diets, the rats are killed, and mammary tumors are counted and classified by histologic type. Cumulative tumor incidence is evaluated by the Kaplan-Meier life-table method and the logrank test. Tumor number is evaluated by the chi-squared test of association, and tumor multiplicity is evaluated by the Mantel-Haenszel chi-squared test. All statistical tests are two-tailed.

The experiment was undertaken with the belief that the addition of an insoluble (wheat bran) fiber and a water soluble cellulose derivative to a high-fat would provide a tumor-inhibiting effect in this mammary tumor model.

To further determine if colon cancer risk reduction by dietary fiber is possible, a comparison of psyllium (PS), a partially fermentable viscous fiber, to methylcellulose (MC), a nonfermentable viscous fiber, in combinations with wheat bran (WB), in an animal model of colon cancer was conducted.

Methods: Male Fisher 344 rats were randomized into 7 groups of 10 animals each and fed for 26 weeks diets containing one of the following fiber sources (8% w/w) in a semi-purified dietary base: WB, microcrystalline cellulose (C), MC, WB:PS (1:1),

or WB:MC (1:3,1:1, and 3:1). The rats were injected with azoxymethane, 15 mg/kg s.c., on weeks 5 and 6. Rats were killed by CO2 inhalation, and colon, liver, and blood samples were obtained. ACFs were quantitated from methylene blue stained, formalin fixed sections by a blinded observer.

Results: As expected, inclusion of PS increased colon weight; MC did not. The proportion of large *vs.* small ACFs did not vary by colon segment or diet. The WB diet showed the lowest number of ACFs (78±7, mean±SE), similar to C (87±8), while the WB:PS and 3:1 WB:MC diets were significantly higher (133±9 and 106±9, resp., $p<0.05$). MC alone was also significantly higher (119±11) *vs.* WB; however, 1:1 and 1:3 mixtures of WB and MC were as effective as WB alone. All three combinations of WB with MC yielded significantly fewer ACFs than the WB:PS diet.

Conclusions: It has been hypothesized that fermentation products of soluble fiber, particularly butyrate, are responsible for its protective effect. These results suggest that fermentation alone cannot account for reduced ACF formation. If fermentation were important, one would not expect the observed outcome for the WB:MC diets in comparison to the WB:PS diet. While not suggesting a particular mechanism of action, sustained viscosity and/or water holding capacity may be critical properties of a soluble fiber with respect to chemoprotection. Furthermore, since the American diet and that of many other cultures typically contains wheat bran, these results support the claim that a supplement which provided only the soluble cellulose derivative would also be protective.

FORMULATIONS

In order to use a water-soluble non-fermentable cellulose derivative as a dietary component, it will normally be used as is, or they may be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice.

The cellulose derivatives may conveniently be administered orally, in a number of ways. They may be administered in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the final desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of "active ingredient" with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being

compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, or nonaqueous liquid suspension.

An effective oral dosage regimen in a human would range from about 0.4 to about 30 grams per day, preferably from about 0.5 to about 20 gram/day, more preferably from about 1.0 grams to about 10 grams/day. Preferably, the minimum intake is greater than 2-3 grams/day.

The dry weight of a typical of an adult human diet is about 500 g/day, and should include at least about 25-30 g of fiber. A healthy human diet should contain at least about 5-6% fiber by weight. A typical U.S. diet contains about half this level. The present invention while making up the fiber intake deficit present in the current human diet with water soluble cellulose derivative will help to reduce cancer risk. It is recognized that while cellulose derivatives may also be protective when added to diets with recommended levels of fiber, the benefit would will most likely be most notable in people who habitually eat less fiber than they should.

It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses given per day can be ascertained by those skilled in the art.

A suitable, alternative formulation for use herein includes, but is not limited to the fast dissolving methylcellulose tablets as described in Daggy et al., PCT/US98/17405, filed 8/21/98, or PCT/US98/17440, filed 8/21/98, whose disclosures are incorporated herein by reference in their entirety.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the are can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed Is:

1. A method of reducing the incidence of colorectal cancers in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a water soluble, non-fermentable cellulose derivative, alone or in combination with an insoluble fiber and/or a soluble fermentable fiber.

2. The method according to Claim 1 wherein the water soluble, non-fermentable cellulose derivative is a cellulose ether which is methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropyl-methylcellulose, or a combination thereof.

3. The method according to Claim 1 or 2, wherein the soluble fermentable fiber is pysllium.

4. The method according to Claim 1 or 2, wherein the insoluble fiber is wheat bran.

5. The method according to any one of Claims 1 to 4 wherein the water soluble, non-fermentable cellulose derivative is methylcellulose or hydroxypropyl-methylcellulose.

6. The method according to Claim 2 wherein the cellulose is administered as bulk powder, a tablet, or suspension, which optionally contains sugar.

7. The method according to Claim 6 wherein the cellulose is administered in a rapidly disintegrating tablet.

8. The method according to Claim 1 wherein the total daily dosage administered is from about 0.4 gram to 30 grams day.

9. The method according to Claim 8 wherein the total daily dosage administered is from about 1 gram to 10 grams day.

10. A method of reducing the incidence of breast cancer in a mammal in need thereof, which method comprises administering to said mammal an effective amount

PCT/US 99/01377
IPEA/US 14 DEC 1999

of a water soluble, non-fermentable cellulose derivative, alone or in combination with an insoluble fiber and/or a soluble fermentable fiber.

11. The method according to Claim 10 wherein the water soluble, non-fermentable cellulose derivative is a cellulose ether which is methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropyl-methylcellulose, or a combination thereof.

12. The method according to Claim 10 or 11, wherein the soluble fermentable fiber is pysllium.

13. The method according to Claim 10 or 11, wherein the insoluble fiber is wheat bran.

14. The method according to any one of Claims 10 to 13 wherein the water soluble, non-fermentable cellulose derivative is methylcellulose or hydroxypropyl-methylcellulose.

15. The method according to Claim 11 wherein the cellulose is administered as bulk powder, a tablet, or suspension, which optionally contains sugar.

16. The method according to Claim 15 wherein the cellulose is administered in a rapidly disintegrating tablet.

17. The method according to Claim 10 wherein the total daily dosage administered is from about 0.4 gram to 30 grams day.

18. The method according to Claim 17 wherein the total daily dosage administered is from about 1 gram to 10 grams day.

Docket No.:C75087

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

" CELLULOSE DEFIVATIVES AND COLORECTAL CANCER RISK REDUCTION"

the specification of which (check one)
[] is attached hereto.
[X] was filed on **21 January 1999** as Serial No. **PCT/US99/01377**
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
60/072,370	**23 January 1998**

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the

States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: **Bruce Paul Daggy**

Inventor's Signature: ______________________

Date: 16 FEB 1999

Residence: 7 Rutledge Road, Pine Brook, New Jersey 07058 NJ

Citizenship: United States of America

Post Office Address: SmithKline Beecham Corporation
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Full Name of Inventor: **Kenneth G. Mandel**

Inventor's Signature: ______________________

Date: 16 FEB 1999

Residence: 9 Doric Avenue, Parsippany, New Jersey 07054 NJ

Citizenship: United States of America

Post Office Address: SmithKline Beecham Corporation
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Stephen Venetianer	Registration No. 25,659
Janice E. Williams	Registration No. 27,142
James M. Kanagy	Registration No. 29,550
William T. King	Registration No. 30,954
Linda E. Hall	Registration No. 31,763
Mary E. McCarthy	Registration No. 32,917
Charles M. Kinzig	Registration No. 33,252
Dara L. Dinner	Registration No. 33,680
Yuriy P. Stercho	Registration No. 33,797
Kirk Baumeister	Registration No. 33,833
Wayne J. Dustman	Registration No. 33,870
William T. Han	Registration No. 34,344
Nora Stein-Fernandez	Registration No. 36,689
Soma G. Simon	Registration No. 37,444
Edward R. Gimmi	Registration No. 38,891
Zoltan Kerekes	Registration No. 38,938

Address all correspondence and telephone calls to **Dara L. Dinner** at Corporate Intellectual Property, UW2220, SmithKline Beecham Corporation, 709 Swedeland Road, King of Prussia, PA 19406-0939, whose telephone number is 610-270-5017.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United